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출혈성 경향이 높은 소아환자의 지속성 신대체 요법시 사용되는 항응고제로서 Nafamostat mesilate의 사용

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The Use of Nafamostat Mesilate as an Anticoagulant during Continuous Renal Replacement Therapy for Children with a High Risk of Bleeding

Purpose: Nafamostat mesilate (NM), a synthetic serine protease inhibitor, has been investigated as an anticoagulant for adult patients with a high risk of bleeding, who need chronic renal replacement therapy (CRRT). However, little is known about the use of NM as an anticoagulant in pediatric CRRT. The aim of this study was to evaluate the ideal dosage, efficacy, and safety of NM in pediatric CRRT.

Methods: We conducted a retrospective study of 40 pediatric patients who had undergone at least 24 h of venovenous CRRTs between January 2011 and October 2013. We divided the patients according to risk of bleeding. Those at high risk received no anticoagulation (group 1) or NM as an anticoagulant (group 2), while those at low risk received heparin (group 3).

Results: Forty patients (25 male and 15 female; mean age, 8.2±6.6 years) were enrolled. The mean duration of CRRT was 13.0 days, and the survival rate was 57.5%. The mean hemofilter lifespan was 39.3 h in group 1 and 11.3 h in group 3. In group 2, hemofilter lifespan was extended from 7.5 h to 27.4 h after the use of NM (P=0.001). The mean hemofilter lifespan with NM was greater than with heparin (P=0.018). No patient experienced a major bleeding event during treatment with NM.

Conclusion: NM may be a good alternative anticoagulant in pediatric patients with a high risk of bleeding requiring CRRT, and is not associated with bleeding complications.

Key words: Nafamostat mesilate, Continuous renal replacement therapy, Children, Bleeding risk

Introduction

With the development of the equipment and techniques has the continuous renal replacement therapy (CRRT) been widely used in pediatric patients with acute kidney injury (AKI) and hemodynamic instability [1-3]. CRRT may be a more appropriate method if a small patient cannot tolerate rapid fluid removal and electrolyte shifts or is not feasible in fluid restriction [4-6]. Critically ill patients may develop a pro-coagulant state due to an early sepsis, hyperviscosity syndromes or antiphospholipid antibodies and an appropriate anticoagulantion with an optimal anti-thrombotic activity and minimal bleeding complication is an important condition for a successful CRRT [7]. Usually, unfractionated heparin has been used, however, it is difficult to administer systemic heparin in critically ill patients who have developed or are at risk of bleeding [8]. Although anticoagulation-free CRRT has been associated with acceptable hemofilter lifespan in patients at high risk of bleeding, some patients experience at least an inevitable clotting of the filter without anticoagulation [8]. The prevention of extracorporeal filter clotting is an important factor in CRRT to reduce frequent circuit changes or blood loss. Therefore, an adequate circuit lifespan is of practical concern for critical care providers and an alternative anticoagulant is necessary for patients with a high risk of bleeding.

Nafamostat mesylate (SK Chemicals Life Science Bizl., Soeul, Korea; licensed by Torli Pharmaceutical Co., Ltd., Tokyo, Japan, 6-amidino-2-naphthyl para-guanidinobenzoate) (NM) is a synthetic serine protease inhibitor that inhibits coagulation and fibrinolysis by inactivating thrombin, plasmin, trypsin, kallikrein, coagulation factors XIIa and Xa and complements [9]. It has such activities as anti-coagulant effect, anti-fibrinolytic activity and anti-platelet actions [9]. The half-life is about 8 minutes and the clearance is performed by dialysis. Although NM was introduced as an alternative anticoagulant for CRRT in 1990, its use is mainly limited to Japan today [8]. Recently is has been prevalently and concomitantly used with unfractionated heparin as an anticoagulant for patients with hemodialysis [9]. However, there are little reports about pediatric dosages and the efficacy of NM with an insufficient proof as an anticoagulant in CRRT [10-13]. The aim of this study was to evaluate the ideal dosage, efficacy and safety of NM in pediatric patients requiring CRRT and with a high risk of bleeding.

Materials and methods

1. Patients

We conducted a retrospective study in pediatric patients (≤18 years old) who underwent at least 24 hours of venovenous CRRT in pediatric intensive care units at the Samsung Medical Center in Seoul, Korea, from January 2011 to October 2013. Medical records were reviewed to obtain the data including age, sex, underlying disease, etiology of AKI, survival, duration of CRRT, prescription of CRRT, hemofilter lifespan, laboratory data and complications associated with anticoagulation. Survival was defined as successful discharge throughout entire hospitalization. The high risk of bleeding was defined as the presence of a prolonged prothrombin time international normalized ratio (PT INR) >2, activated partial thromboplastin time (aPTT) >60 seconds, platelet counts <50,000/mm^3, activated clotting time (ACT) ≥200 seconds, major surgery within seven days before CRRT, brain hemorrhage or an operation within 14 days before CRRT. We divided the patients into the group with a high risk of bleeding (group 1=no anticoagulation and group 2=NM as an anticoagulant) and no risk of bleeding (group 3= unfractionated heparin as an anticoagulant).

2. Continuous renal replacement therapy

The modality of CRRT was an exclusively continuous venovenous hemodiafiltration. All CRRT were performed using Prisma (n=31, Gambro Healthcare, Lakewood, CO, USA) or Prismaflex (n=9, Gambro Healthcare) machines. Vascular access was performed by the insertion of a double-lumen catheter with 8 to 11 Fr diameter (Gambro Healthcare) into the internal jugular or femoral vein. The

polyacrylonite hollow-fiber hemofilter (M-60/100 or ST-60/100, Gambro) was initially used in all patients. This hemofilter was replaced with an ST-60 or ST-100 when NM was infused. Commercially prepared bicarbonate-buffered replacement fluid (Hemosol B0, Gambro Korea, Seoul, Korea) was used for dialysate and replacement fluid. The blood flow rate was determined as 3 to 5 mL/kg/min. The predilution replacement fluid rate or dialysate rate was introduced at a rate of 2,000 mL/1.73 m^2/hour. The patient fluid removal rate was determined by the degree of fluid overload.

3. Anticoagulation protocol

In our study, the infusion rate of NM was adjusted according to the protocol for pediatric patients (Fig. 1). In the groups with a high risk of bleeding, we started CRRT without anticoagulation, and NM was only used if the initial hemofilter lifespan was less than 12 hours or ACT was less than 200 seconds. The NM regimen was a continuous infusion (200 mg of NM mixed with 20 mL of 5% dextrose solution) and started at the rate of 0.25 mg/kg/hour. The NM infusion rate was adjusted according to circuit ACT values drawn through an arterial line. Plasma ACT was measured before CRRT and 4 hours, 8 hours and 24 hours after CRRT start. From the next day onwards, samples for ACT were drawn every 24 hours. The infusion rate of NM was adjusted targeting the dosage with a hemofilter lifespan longer than 12 hours under ACT less than 120% of the starting value. The infusion rate of NM was doubled if the hemofilter lifespan was shorter than 12 hours under ACT less than 120% of the starting value. The infusion rate of NM was reduced to 50% of the previous dosage if the circuit ACT was prolonged to more than 120% and less than 150% of the starting value. The NM infusion was discontinued for two consecutive hours, if the circuit ACT was more than 150% of the starting value or above 200 seconds. In patients without bleeding risk, unfractionated heparin was continuously infused for anticoagulation with 10 U/kg/hour after a 20 U/kg initial bolus. Plasma aPTT was measured every 6 hours and the infusion rate of heparin was adjusted targeting an aPTT of 45 to 60 seconds. The hemofilter systems were routinely changed every 72 hours.

4. Efficacy and safety of nafamostat mesilate

The efficacy of NM was assessed by the hemofilter lifespan before and after NM infusion in group 2. The hemofilter lifespan was also estimated and compared between the group with NM and the group with heparin. To assess the safety of NM, we reviewed the adverse events including major bleeding, agranulocytosis, hyperkalemia or anaphylaxis.

5. Statistical Analysis

Values are expressed as means with standard deviation. The comparison of the mean hemofilter lifespan between before and after NM infusion in group 2 was performed using Wilcoxon signed rank test. The comparisons of the mean hemofilter lifespan of all groups were performed using ANOVA. A *P*-value of less than 0.05 was considered statistically significant. We used a commercially available statistical package (PASW 17, SPSS Inc., Chicago, IL, USA).

Results

1. Baseline characteristics of all patients

During the study period, 57 pediatric patients received CRRT and 40 patients were enrolled in the present study (Table 1). Seventeen patients were not included because of short CRRT duration less than 24 hours. The study subject group with 40 patients consisted of 25 males and 15 females with a mean age of 8.2±6.6 years. Underlying diseases were as follows: hematologic diseases including malignancy in 23 patients (57.5%), solid malignancy in 3 patients (7.5%), chronic kidney disease in 3 patients (7.5%) and sepsis in 1 patient (2.5%). Etiologies of AKI were as follows: sepsis in 12 patients (29.7%) and tumor lysis syndrome or rhabdomyolysis in 11 patients (29.7%). The duration of CRRT was 13.0±23.5 days. The

survival rate was 57.5 %.

2. Comparison of the parameters among the 3 groups

A total of 34 (85%) patients with a high risk of bleeding were assigned to start CRRT without anticoagulation. Of them, 19 patients (55.8%) continued CRRT without anticoagulation (group 1), and NM was started in 15 patients (44.1%) in whom the hemofilter lifespan was initial less than 12 hours or ACT was less than 200 seconds (group 2). Six patients were assigned to start CRRT with heparin anticoagulation (group 3).

There was no significant difference in age, sex, underlying diseases, cause of AKI, survival, duration of CRRT, blood flow rate and laboratory findings (Table 2). While sepsis was the most common cause of AKI in group 1, tumor lysis syndrome and/or rhabdomyolysis were the most common causes of AKI in group 3. Platelet counts were lower in group 1 and 2 than in group 3, but there was no statistical significance. The levels of aPTT and ACT were more prolonged in group 1 and 2 than in group 3 but there was no statistical significance. Group 3 showed a tendency of shorter CRRT duration and good survival without significant difference.

Table 1. Baseline Characteristics of the Enrolled Patients

Characteristics	All patients (n=40)
Age (year)	8.2±6.6
Male: Female	25:15
Underlying disease n (%)	
Hematologic disease/malignancy	23 (57.5)
Solid malignancy	3 (7.5)
Chronic kidney disease	3 (7.5)
Sepsis	1 (2.5)
Others	10 (25)
Causes of AKI n (%)	
Sepsis	12 (29.7)
TLS/Rhabdomyolysis	11 (29.7)
Others	17 (40.5)
Duration of CRRT (days)	13.0±23.5
Survival (%)	57.5

Data are expressed as mean±standard deviation.
Abbreviations: TLS, Tumor lysis syndrome; AKI, Acute kidney injury; CRRT, Continuous renal replacement therapy.

3. The efficacy and safety of NM

Before the use of NM, there was a significant difference in the hemofilter lifespan among the 3 groups (group 1 39.3±24.3 hours; group 2 7.5±3.0 and group 3 11.3±4.5

Table 2. Comparisons of the Basal Parameters among 3 Groups

Characteristics	Group 1 (n=19) Anticoagulation-free	Group 2 (n=25) NM	Group 3 (n=6) Heparin
Age (year)	9.2±6.4	6.9±5.6	9.2±9.8
Male: Female	12: 7	9: 6	4: 2
Underlying disease n (%)			
Hematologic malignancy	10 (52.6)	10 (66.6)	3 (50.0)
Solid malignancy	2 (10.5)	1 (6.6)	0 (0)
Chronic kidney disease	1 (5.2)	1 (7.1)	1 (16.6)
Sepsis	1 (5.2)	0 (0)	0 (0)
Others	5 (26.3)	3 (0.2)	2 (33.2)
Causes of AKI n (%)			
Sepsis	7 (36.8)	4 (26.6)	1 (16.6)
TLS/Rhabdomyolysis	3 (15.7)	4 (26.6)	4 (66.6)
Others	8 (42.1)	7 (46.6)	1 (16.6)
Platelet count (x1,000/mm^3)	36.7±21.6	43.2±23.4	328.0±185.3
PT INR	1.7±0.7	1.4±0.3	1.3±0.2
aPTT (seconds)	73.9±74.7	50.8±23.5	45.2±11.2
ACT (seconds)	206	124.9±19.5	93.0±36.1
Blood flow rate (ml/min)	91.1±45.9	90.0±44.2	98.2±48.8
Duration of CRRT (days)	8.6±8.0	22.7±35.8	2.8±1.2
Survival (%)	42.1	60	100

Data are expressed as mean±standard deviation.
Abbreviations: NM, Nafamostat mesilate; AKI, Acute kidney injury; TLS, Tumor lysis syndrome; PT INR, Prothrombin time international normalized ratio; Activated partial thromboplastin time, aPTT; Activated clotting time, ACT; CRRT, Continuous renal replacement therapy.

hours, *P*=0.000) and the patients in group 2 showed a relatively shorter hemofilter lifespan compared with that of group 1 and 3 (Fig. 1). However, after the use of NM, the mean hemofilter lifespan with NM was significantly greater than that of heparin (*P*=0.018) (Fig. 2). The hemofilter lifespan in group 1 was greater than that of group with NM or heparin. In group 2, the hemofilter lifespan was significantly lengthened after the use of NM from 7.5±3.0 to 27.4±19.0 hours (*P*=0.001) (Fig. 3). There was no report of adverse events associated with NM including major bleeding, agranulocytosis, hyperkalemia and anaphylaxis.

Discussion

CRRT accounts for a majority of renal replacement therapy performed in pediatric patients with AKI and hemodynamic instability. Prisma machines are only used with predilution mode and Prismaflex have both predilution and postdilution modes. The risk of bleeding is high in critically ill patients due to the disruption of

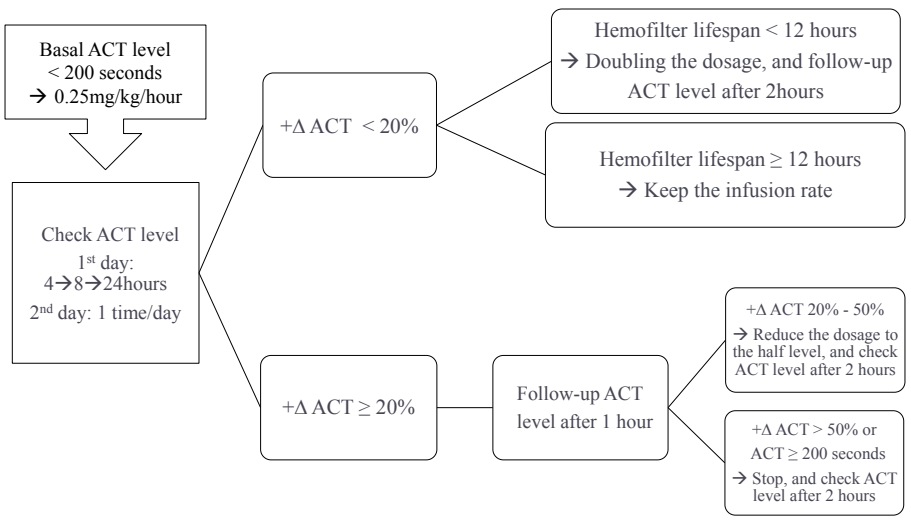

Fig. 1. The flow diagram for a continuous infusion of nafamostat mesilate for pediatric patients with a high risk of bleeding and a short hemofilter lifespan.

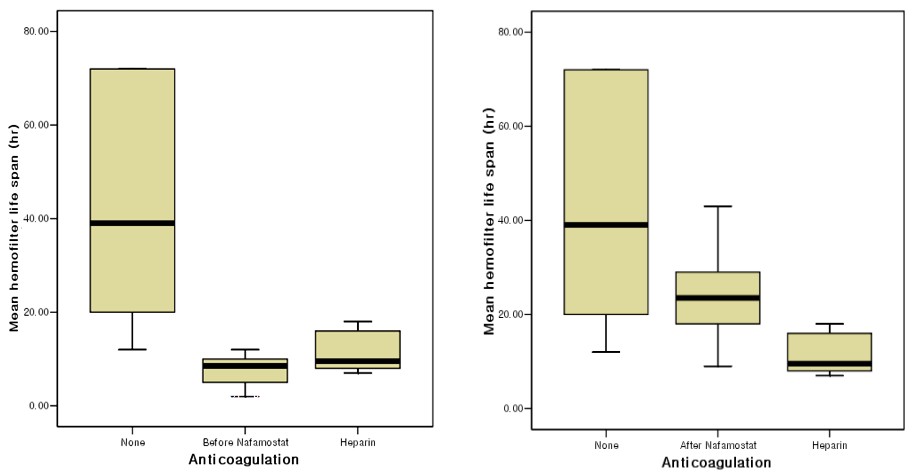

Fig. 2. The comparison of mean hemofilter lifespans before (left) and after the use of nafamostat mesilate (right) among 3 groups. The hemofilter lifespan after nafamostat mesilate in group 2 was significantly greater than that in the group with heparin (*P*=0.018).

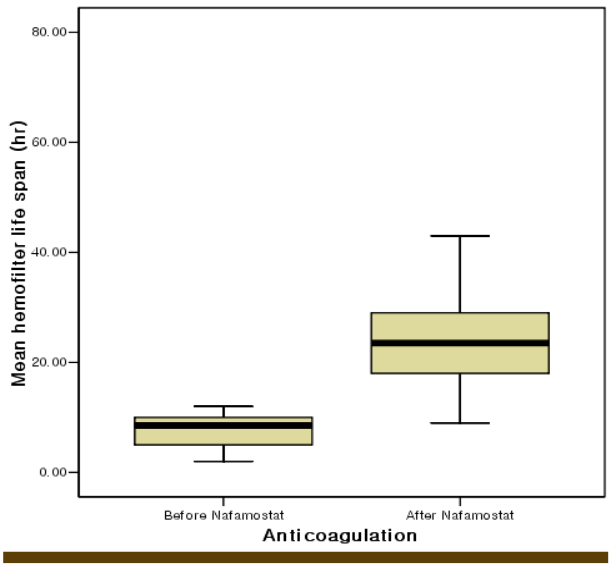

Fig. 3. The comparison of mean hemofilter lifespans before and after nafamostat mesilate infusion in group 2. The hemofilter lifespan significantly increased after the infusion of nafamostat mesilate (P=0.001).

the integrity of vascular wall and coagulopathy, and the concern for complications associated with anticoagulation may be an obstacle for CRRT. Therefore, the use of an appropriate anticoagulant is necessary for CRRT. The conditions for an ideal anticoagulation include optimal anti-thrombotic activity with minimal bleeding complications, less systemic effects and a short half-life [14].

There were some papers reporting the use of MN in adult CRRT, but little published data on the use of NM as an anticoagulant in pediatric CRRT. Our study focused on the ideal dosage for pediatric patients as well as on the efficacy and safety of NM in pediatric CRRT. The hemofilter lifespan was used as a parameter for the effectiveness of NM, because the hemofilter lifespan is an important factor in reducing the number of times for preparation and set-up of CRRT as well as in the containment of costs associated with the use of circuit components and membranes [15]. An adequate circuit life would ideally require the use of one circuit per day to achieve treatment efficiency and reduce expenses and demand on nursing time resetting the circuit [15]. This goal may be achieved when the circuit life is between 18 and 30 hours [15]. The efficacy to stabilize or reduce plasma urea and creatinine concentrations was threatened when the treatment was interrupted and the actual delivered treatment within a 24 hour cycle was shown to be less than 16 hours [15]. In group 2, our study showed that a continuous infusion of NM lengthened the mean hemofilter lifespan from 7.5 to 27.4 hours without significant bleeding. In another retrospective cohort study, it was also shown that NM significantly lengthened hemofilter lifespan without causing bleeding complications in spite of the prolongation of aPTT [16]. Therefore, we suggest that NM can be used as an effective anticoagulant to keep the adequate circuit life in both, adult and pediatric patients.

There were little data regarding the ideal dosage of NM in pediatric CRRT. Some reports suggest the dosage of NM as 0.1 to 1 mg/kg/hour targeting the levels of ACT between 150 and 200 seconds [13, 17]. There was another report suggesting the dosage of NM as 0.48 mg/kg/hour with unfractionated heparin (21 U/kg/hour) to keep the levels of ACT between 190 and 220 seconds in neonate [18]. Although these studies were not performed for the pediatric CRRT, we designed our NM protocol on the basis of these studies because of a lack of data. We proposed the adequate dosage of NM and the available parameter to prevent bleeding and keep the hemofilter lifespan.

There were a few reports of anaphylactoid reactions regarding the use of NM [19-21]. Hyperkalemia has been reported as another adverse effect of NM [22, 23]. In our study, no patient experienced a major bleeding complication, agranulocytosis, hyperkalemia or an anaphylaxis associated with NM. Therefore, the NM protocol in our study seems to suggest effectiveness and safety in pediatric patients with a high risk of bleeding.

In group 1, there was no necessity of anticoagulation for CRRT. It is an important finding that approximately 85% of our pediatric patients presented with the condition of a high bleeding risk at the beginning of CRRT. Nineteen patients (55.8%) of them could be managed without anticoagulation and the mean hemofilter lifespan was 39.3 hours. They had to some degree an innate anticoagulation relation to the prolonged PT INR, aPTT and low platelet counts associated with their underlying disease. This might suggest that anticoagulation-free CRRT can be considered in critically ill pediatric patients

at a high risk of bleeding and NM maybe selectively applied in those patients who had an initial short hemofilter lifespan [7].

AN-69 membrane has been known that it is associated with bradykinin release syndrome. The negatively charged membrane AN69 is known to evoke anaphylactoid reactions [24]. However, the NM can be used in positively charged ST membrane. We had experienced no anaphylactoid reaction during the use of NM with ST membrane.

Our study had several limitations. First, it was a single center and retrospective study with a small number of patients. Second, we were not able to apply the same catheter-size and vascular access to all pediatric patients and it is possible that the differences in the catheter sizes and vascular accesses may have influenced the hemofilter lifespan. Third, the replacement fluid was only delivered by a predilution mode, which has been introduced as a useful adjunct to prevent clotting of the extracorporeal circuit and to extend the filter life [7]. Therefore, our results have its limitations to be applied to patients who need CRRT with replacement fluid delivered by postdilution mode.

In conclusion, CRRT without anticoagulation could be considered in pediatric patients at a high risk of bleeding. As an alternative anticoagulation, continuous infusion of NM lengthened the hemofilter lifespan without significant complications in pediatric patients with the high risk of bleeding and a short filter lifespan.

한글요약

목적: Nafamostat mesilate는 출혈성 경향이 있는 성인 환자에서 지속적 신대체 요법시 항응고제로 사용되고 있지만 소아에서의 경험은 잘 알려지지 않았다. 본 연구는 출혈성향이 높은 소아에서 지속적 신대체 요법을 시행하는 경우에 항응고제로서 Nafamostat mesilate의 용량, 효과, 및 안전성에 대하여 알아보기 위해 수행하였다.

방법: 2011년 1월부터 2013년 10월까지 최소 24시간이상 지속적신대체요법을 받은 40명의 소아환자들을 대상으로 하여 의무기록을 후향적으로 분석하였다. 환자들은 출혈 위험군(그룹 1: 항응고제 사용 안함, 그룹 2: 항응고제로 Nafamostat mesilate 사용)과 출혈 위험이 없는 군(그룹 3: 항응고제로 헤파린 사용)으로 분류하였다.

결과: 40명의 환자 중에서 남아는 25명 여아는 15명 이었으며 평균 나이는 8.2±6.6세 이었다. 지속적신대체요법의 평균 시간은 13일 이었다. 평균 혈액 필터 수명은 그룹 1에서는 39.3시간 이었고, 그룹 3에서는 11.3시간이었다. 그룹 2에서는 Nafamostat mesilate 사용 전에는 7.5시간 이었으나 Nafamostat mesilate 사용 후에는 27.4시간으로 연장되었으며 통계학적으로 유의하였다(P=0.001). 평균 혈액 필터 수명은 Nafamostat mesilate을 사용한 그룹에서는 헤파린을 사용한 그룹보다 통계적으로 의미 있게 연장되었다(P=0.018). Nafamostat mesilate 사용한 군에서 의미있는 출혈이 동반되지는 않았다.

결론: Nafamostat mesilate은 출혈 성향이 높은 소아에서 지속적 신대체 요법을 시행하는 경우에 헤파린을 대체해서 사용될 수 있는 항응고제로 생각된다.

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Disclosure Statement

The authors have no conflicts of interest to disclosure.

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